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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/748,853 | 12/30/2003 | Carl J. Wheeler | VICAL1380-2 | 6433 |

28213 7590 08/04/2009

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| EXAMINER | |
|---|---|
| ROYDS, LESLIE A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1614 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 08/04/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/748,853 | WHEELER, CARL J. | |
| | Examiner | Art Unit | |
| | LESLIE A. ROYDS | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *68,71-74 and 85-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *68,71-74,85-87* is/are rejected.

7)☒ Claim(s) *68 and 85* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

**Claims 68, 71-74 and 85-87 are presented for examination.**

A request for continued examination under 37 C.F.R. 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. 1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 C.F.R. 1.114. Applicant's payment filed June 29, 2009 has been received and entered into the present application. Accordingly, prosecution has been reopened.

Claims 68, 71-74 and 85-87 remain pending and under examination. Claims 64-67, 69-70, 75-84 and 88-90 are cancelled. Claims 68 and 85-86 are amended.

Applicant's arguments, filed June 29, 2009, have been fully considered. Rejections and objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and objections are either reiterated or newly applied. They constitute the complete set of rejections and objections presently being applied to the instant application.

### *Objection to the Claims (New Grounds of Objection)*

Claim 68 and 85 are objected to for reciting sulfur twice as an option for Z in each of the claims.

### *Claim Rejections - 35 USC § 112, Second Paragraph (New Grounds of Rejection)*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 68 and 85-86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired.

Instant claim 68 recites that $R_1$ and $R_2$ are, independently, selected from hydrogen, linear or branched, unsubstituted or substituted $C_{1-23}$ alkyl, acyl, alkenyl, or heteroalkyl group having from 0-6 sites of unsaturation, etc. However, the claim also states that $R_1$ and $R_2$ are identical and are selected from the group consisting of $C_{14}H_{29}$ and $C_{12}H_{25}$. The two limitations conflict because the first limitation provides for $R_1$ and $R_2$ to be independently selected from numerous possible substituents, but the second limitation provides for $R_1$ and $R_2$ to be identical and selected from only two alkylene options. In other words, the first limitation is a broader recitation of the possible substituents for either $R_1$ or $R_2$, but the second limitation is a narrower statement of the possible substituents for $R_1$ and $R_2$. The fact that these two limitations co-exist in the same claim renders the claim indefinite because it is unclear which phrase is actually meant to limit the instantly claimed subject matter. Accordingly, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the scope of subject matter for which Applicant is presently seeking protection. Clarification is requested.

Instant claim 85 recites that Z is selected from the group consisting of oxygen, sulfur, $NR_1$ and NH. However, the claim also states that Z is NH or $NR_1$. The two limitations conflict because the first limitation provides for several options for Z (i.e., oxygen, sulfur, $NR_1$ and NH), but the second limitation provides for Z only to be selected from either NH or $NR_1$. In other words, the first limitation is a broader recitation of the possible substituents for Z, but the second limitation is a narrower statement of the possible substituents for Z. The fact that these two limitations co-exist in the same claim renders the claim indefinite because it is unclear which phrase is actually meant to limit the instantly claimed subject matter. Accordingly, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the scope of subject matter for which Applicant is presently seeking protection.

Clarification is requested.

Finally, instant claim 86 recites an extensive generic formula of possible compounds that may be used to form a lipid complex. However, confusingly, the claim then recites several species of compounds encompassed by the larger generic formula. In other words, the first limitation is a broader recitation of the possible compounds that may be used, but the second limitation is a narrower statement of the possible compounds that may be used in the context of the instantly claimed method. The fact that these two limitations co-exist in the same claim renders the claim indefinite because it is unclear which phrase is actually meant to limit the instantly claimed subject matter. Accordingly, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the scope of subject matter for which Applicant is presently seeking protection.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

For the purposes of examination and the application of prior art, the instant claims will be interpreted to circumscribe the broader scope of subject matter recited in each claim.

***Claim Rejections - 35 USC § 103 (New Grounds of Rejection)***

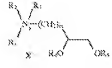
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 68 and 85-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nantz et al. (U.S. Patent No. 5,869,715; Issued 1999, Filed September 1995, already of record) in view of Felgner (WO 91/17424; 1991, already of record).

Please note that, for the purposes of the instant rejection, the instant claims are interpreted to circumscribe the broader scope of subject matter recited in each of claims 68 and 85-86 that have the ambiguity discussed above under 35 U.S.C. 112, second paragraph.

Nantz et al. teaches cationic lipid compounds that are functional to bind and transport polynucleotides, polypeptides, pharmaceutically substances and other biologically active species through membrane barriers (col.1, l.6-9), wherein the cationic compounds are of the following chemical structure:



, wherein $R_4$ and $R_5$ may each be, *inter alia*, alkyl; m is 1-10; $R_1$ and $R_3$ may each be, *inter alia*, alkyl; X is an anion; and $R_2$ may be, *inter alia*, acyl or acyloxy containing alkyl group (col.3, l.42-67).

The cationic lipid compounds disclosed by Nantz et al. correspond to Applicant's instantly claimed compounds, wherein $R_1$ and $R_2$ are each independently a linear or branched, unsubstituted or substituted $C_{1-23}$ alkyl; n is 1-6; $R_3$ and $R_4$ are each independently a linear or branched, unsubstituted or substituted $C_{1-23}$ alkyl; m is 1-10; Z is oxygen; and $R_6$ is hydrogen or equivalent to $R_1$, $R_2$, $R_3$ or $R_4$ (i.e., in this case, $R_6$ may be linear or branched, unsubstituted or substituted $C_{1-23}$ alkyl).

Nantz et al. fails to explicitly teach the step of combining the disclosed cationic lipid compounds with an anionic molecule to deliver the anionic molecule into a cell (claims 64 and 71).

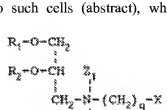
Felgner teaches that cationic lipid technology using positively charge synthetic cationic lipids in the form of liposomes, or small vesicles, is capable of interacting spontaneously with DNA, which is negatively charged, or anionic, to form lipid-DNA complexes having a net positive charge and are capable of fusing with the negatively charged cell membranes of tissue culture cells to achieve both uptake and expression of the DNA by said cells (p.2, l.28-p.3, l.3). Felgner further teaches that valuable therapeutic agents are most effective in influencing cell function at the subcellular or molecular levels (such as, e.g., natural biological molecules and their analogues or foreign substances, such as drugs) and

are, therefore, preferably incorporated into the cell in order to produce their effect (p.1, l.13-24). Still further, Felgner discloses that intracellular delivery of bioactive agents is particularly useful for, e.g., introducing expressible DNA and mRNA into the cells of a mammal to effect intracellular delivery of beneficial or interesting proteins (p.2, l.1-8).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to employ the cationic lipid compounds as disclosed by Nantz et al., which are expressly taught to be useful for binding and transporting polynucleotides, polypeptides, pharmaceutically substances and other biologically active species through membrane barriers, in the form of liposomes and combining such liposomes with anionic DNA (i.e., an "anionic molecule" as instantly claimed; see, e.g., instant claim 68) to form a lipid-DNA complex with a net positive charge to elicit the predictable result of fusing with the negatively charged cell membranes of tissue culture cells to transfect such DNA into the cell such that the cell then expresses the DNA. Such a person would have been clearly motivated to do so in order to predictably effect the intracellular delivery of expressible DNA into cells to produce proteins of interest (e.g., proteins of therapeutic value or proteins of experimental value, etc.).

Claims 68, 71-74 and 85-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jessee (WO 95/02698; Published January 1995) in view of Felgner (WO 91/17424; 1991).

Jessee teaches compositions of cationic lipids and viral components that are useful for transfecting eukaryotic cells with nucleic acids (which are large anionic molecules; p.1, p.12-16) and also for the introduction of other macromolecules into such cells (abstract), wherein the cationic lipid



compounds have the following chemical structure: (p.19, l.22-33), wherein $R_1$ and $R_2$ are separately, *inter alia*, $C_{1-23}$ alkyl (i.e., which corresponds to Applicant's instantly claimed

$R_1$ and $R_2$ groups that may be $C_{1-23}$ alkyl as in instant claim 68 or 85-86 or $C_{10-18}$ alkyl as in instant claim 71 or $C_{14}H_{29}$ or $C_{12}H_{25}$ as in instant claim 72), q is 1-6 (i.e., which corresponds to Applicant's instantly claimed m that may be 1-10), $Z_1$ and $Z_2$ are separately, *inter alia*, hydrogen or an unbranched alkyl group of 1-6 carbon atoms (i.e., which correspond to Applicant's instantly claimed $R_3$ and $R_4$ groups that may be hydrogen or $C_{1-23}$ alkyl as in instant claims 68 or 71 or may be $C_{1-5}$ alkyl groups as in instant claim 73 or may be methyl groups as in instant claim 74) and X may be selected from, *inter alia*, carboxyspermine (i.e., which is understood to be a teaching that the carboxy-terminus of the carboxyspermine is attached to the methylene chain $(CH_2)_q$ since it is named first, which also meets Applicant's requirement that $R_5$ has the structure $-C(=O)-Z-R_6$, wherein Z is nitrogen, since the $-Z-R_6$ group would be the spermine chain attached to the carboxy terminus of -C(=O) as recited in instant claim 68 or Applicant's requirement that $R_5$ has the structure $-C(=O)-N-R_7R_8$, wherein the $R_7$ and $R_8$ group would be the spermine chain, which would comprise a hydrogen from the terminal end of the spermine chain as $R_7$ and the remainder of the spermine chain as $R_8$, which is provided for in the instant claims as "other bioactive or pharmaceutical agent" as in instant claim 71; p.19, l.33-40).

Note also that it is understood that, in order to attach the carboxyspermine compound to the end of the methylene group of the remainder of the cationic compound, the compounds would be reacted so as to remove water via the attachment of a hydrogen from the alkyl group at the end of the compound with the -OH group of the carboxyspermine compound such that the carbonyl group of the carboxyspermine compound would be attached directly to the end of the methylene group of the cationic compound (i.e., $-CH_2-C(=O)-$), absent factual evidence to the contrary.

Jessee fails to explicitly teach the step of combining the disclosed cationic lipid compounds with an anionic molecule to deliver the anionic molecule into a cell (claims 68, 71 or 85-86).

Felgner teaches that cationic lipid technology using positively charged synthetic cationic lipids in the form of liposomes, or small vesicles, is capable of interacting spontaneously with DNA, which is

negatively charged, or anionic, to form lipid-DNA complexes having a net positive charge and are capable of fusing with the negatively charged cell membranes of tissue culture cells to achieve both uptake and expression of the DNA by said cells (p.2, l.28-p.3, l.3). Felgner further teaches that valuable therapeutic agents are most effective in influencing cell function at the subcellular or molecular levels (such as, e.g., natural biological molecules and their analogues or foreign substances, such as drugs) and are, therefore, preferably incorporated into the cell in order to produce their effect (p.1, l.13-24). Still further, Felgner discloses that intracellular delivery of bioactive agents is particularly useful for, e.g., introducing expressible DNA and mRNA into the cells of a mammal to effect intracellular delivery of beneficial or interesting proteins (p.2, l.1-8).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to employ the cationic lipid compounds as disclosed by Nantz et al., which are expressly taught to be useful for binding and transporting polynucleotides, polypeptides, pharmaceutical substances and other biologically active species through membrane barriers, in the form of liposomes and combining such liposomes with anionic DNA (i.e., an "anionic molecule" as instantly claimed; see, e.g., instant claim 68) to form a lipid-DNA complex with a net positive charge to elicit the predictable result of fusing with the negatively charged cell membranes of tissue culture cells to transfect such DNA into the cell such that the cell then expresses the DNA. Such a person would have been clearly motivated to do so in order to predictably effect the intracellular delivery of expressible DNA into cells to produce proteins of interest (e.g., proteins of therapeutic value or proteins of experimental value, etc.).

***Conclusion***

Rejection of claims 68, 71-74 and 85-87 is proper.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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July 30, 2009

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